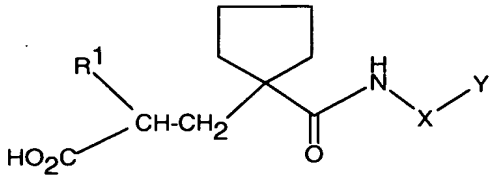
Claims

1 A compound of formula (I), a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof;



(I)

wherein

R^1 is C_{1-6}alkyl which may be substituted by one or more substituents, which may be the same or different, selected from the list: halo, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, carbocyclyl, carbocyclyloxy, C_{1-4}alkoxycarbocyclyloxy, heterocyclyl, heterocyclyloxy, -NR^2R^3, -NR^4COR^5, -$NR^4SO_2R^5$, -$CONR^2R^3$, -$S(O)_pR^6$, -COR^7 and -$CO_2(C_{1-4}$alkyl); or R^1 is carbocyclyl or heterocyclyl, each of which may be substituted by one or more substituents from said list, which substituents may be the same or different, which list further includes C_{1-6}alkyl; or R^1 is hydrogen, C_{1-6}alkoxy, -NR^2R^3 or -$NR^4SO_2R^5$;

wherein

R^2 and R^3, which may be the same or different, are carbocyclyl or heterocyclyl (each of which may be substituted by C_{1-4}alkyl, hydroxy or C_{1-4}alkoxy); or are hydrogen or C_{1-4}alkyl; or R^2 and R^3 together with the nitrogen to which they are attached form a pyrrolidinyl, piperidino, morpholino, piperazinyl or *N*-(C_{1-4}alkyl)piperazinyl group;

R^4 is hydrogen or C_{1-4}alkyl;

R^5 is C_{1-4}alkyl, CF_3, carbocyclyl, C_{1-4}alkylcarbocyclyl, C_{1-4}alkoxycarbocyclyl, heterocyclyl, C_{1-4}alkoxy or -NR^2R^3;

R^6 is C_{1-4}alkyl, carbocyclyl, heterocyclyl or NR^2R^3; and

R^7 is C_{1-4}alkyl, carbocyclyl or heterocyclyl;

p is 0, 1, 2 or 3;

X is the linkage $-(CH_2)_n-$ or $-(CH_2)_q-O-$ (wherein Y is attached to the oxygen); wherein one or more hydrogen atoms in linkage X may be replaced independently by C_{1-4}alkoxy; hydroxy; hydroxyC_{1-3}alkyl; C_{3-7}cycloalkyl; carbocyclyl; heterocyclyl; or by C_{1-4}alkyl optionally substituted by one or more fluoro or phenyl groups; n is 3, 4, 5, 6 or 7; and q is 2, 3, 4, 5 or 6; and

Y is phenyl or pyridyl, each of which may be substituted by one or more groups R^8 which may be the same or different, wherein R^8 is hydroxy; mercapto; halogen; cyano; acyl; amino; mono(C_{1-4}alkyl)amino; di(C_{1-4}alkyl)amino; carbocyclyl or heterocyclyl (either of which is optionally substituted by C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio or halogen); C_{1-6}alkoxy; phenoxy; C_{1-6}alkylthio; phenylthio; or alkyl optionally substituted by C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, halogen or phenyl; or

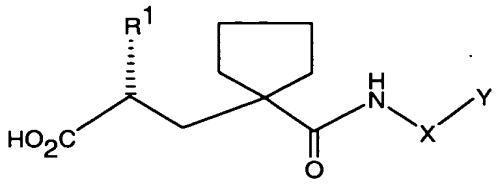
two R^8 groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclyic ring, optionally substituted by C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio or halogen.

2 A compound according to claim 1, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-3}alkyl, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-3}alkyl or C_{1-6}alkyl substituted by phenyl.

3 A compound according to claim 2, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-3}alkyl or C_{1-6}alkoxyC_{1-6}alkoxyC_{1-3}alkyl.

4 A compound according to claim 3, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein R^1 is C_{1-4}alkyl or C_{1-6}alkoxyC_{1-3}alkyl.

5 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, of formula Ia:



(Ia)

6 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof wherein X is $-(CH_2)_n-$ and wherein one or more hydrogen atoms in linkage X may be replaced by one or more of the groups defined claim 1.

7 A compound according to any preceding claim, pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when present n is 3 or 4.

8 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein R^8 is C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, mercapto, halo, cyano, carbocyclyl or heterocyclyl; or two R^8 groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclyic ring, optionally substituted by C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio or halogen.

9 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when R^8 is carbocyclyl, R^8 is cyclopentyl, cyclopropyl, cyclohexyl or phenyl.

10 A compound according to any one of claims 1 to 8, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when R^8 is heterocyclyl, R^8 is pyridyl, oxadiazolyl, pyrazolyl or triazolyl.

11 A compound according to any one of claim 1 to 8, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when Y is phenyl and two R^8 groups on adjacent carbon atoms together with the interconnecting carbon atoms form a fused 5- or 6-membered carbocyclic or

heterocyclyic ring, the fused ring systems are naphthyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, dihydrobenzofuranyl, benzoxazolyl, indanyl, benzisothiazolyl and benzothiazolyl.

12 A compound according to claim 1, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein the compound is:

(*2R*)-2-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-pentanoic acid (Example 16);

3-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]propanoic acid (Example 18);

3-{[1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl]-propanoic acid (Example 21);

2-{[1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-methoxybutanoic acid (Example 15);

2-{[1-({[3-(4-fluorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-methoxybutanoic acid (Example 4);

4-methoxy-2-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]-methyl}butanoic acid (Example 1);

2-{[1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl]-methyl}-4-methoxybutanoic acid (Example 11);

(2S)-2-{[1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-methoxybutanoic acid (Example 22); and

(2S)-2-{[1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl]-methyl}-4-methoxybutanoic acid (Example 25).

13 *(2S)*-2-{[1-({[3-(4-Chlorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-methoxybutanoic acid (Example 22).

14 The use of a compound defined in any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, in the manufacture of a medicament for treating or preventing a condition for which a beneficial response is obtained by the inhibition of neutral endopeptidase.

15 The use according to claim 14 wherein the condition is Female Sexual Dysfunction or Male Erectile Dysfunction.

16 The use according to claim 15 wherein the condition is Female Sexual Arousal Disorder.

17 The use according to any one of claims 14 to 16 wherein the compound is administered systemically.

18 The use according to claim 17 wherein the compound is administered orally.

19 The use according to any one of claims 14 to 16 wherein the compounds are administered topically.

20 A compound defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, for use as a medicament.

21 A method of treating or preventing a condition for which a beneficial response is obtained by the inhibition of neutral endopeptidase in a mammal comprising treating said mammal with a therapeutically effective amount of a compound defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof.

22 The method of claim 21 wherein the condition is defined in claim 15 or 16.

23 A pharmaceutical composition including a compound defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof together with a pharmaceutically acceptable excipient, diluent or carrier.

24 A combination of a compound defined in any one of claims 1 to 13 and one or more active ingredients selected from the list:

a) a PDE5 inhibitor, more preferably 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil); (6R,12aR)-2,3,6,7,12,12a-

hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) - pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one and pharmaceutically acceptable salts thereof;

b) an NPY Y1 inhibitor;

c) a dopamine agonist such as apomorphine or a selective D_2, D_3 or D_2/D_3agonist such as, pramipexole and ropirinol;

d) a melanocortin receptor agonist or modulator or melanocortin enhancer, preferably melanotan II, PT-14, PT-141;

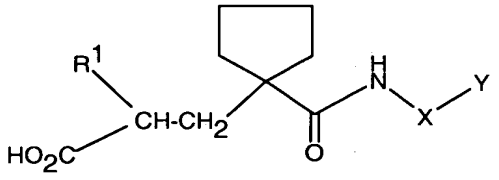
e) an agonist, antagonist or modulator for 5HT2C;

f) an estrogen receptor modulator, estrogen agonists and/or estrogen antagonists, preferably raloxifene, tibolone or lasofoxifene;

g) an androgen such as androsterone, dehydro-androsterone, testosterone, androstanedione and a synthetic androgen; and

h) an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as oestrogen benzoate.

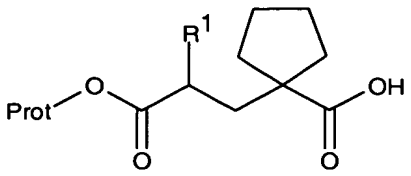
A process for the preparation of a compound of general formula I



(I)

wherein R^1, X and Y are as defined in any one of claims 1 to 13 or salts thereof comprising the steps of:

a) reacting a compound of formula II

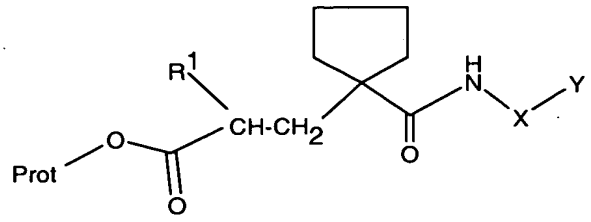


(II)

wherein Prot is a suitable protecting group, with a compound of formula III

$$Y\text{-}X\text{-}NH_2 \qquad (III)$$

to give a compound of formula IV;



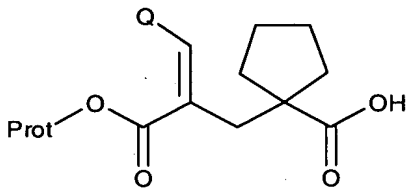
(IV) ;

then

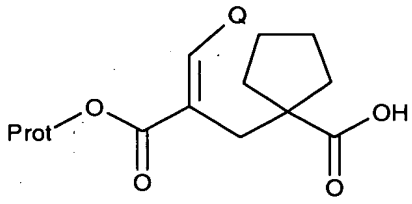
b) reacting compound of formula IV under suitable deprotecting conditions to give the compound of formula I; then

c) optionally forming a salt.

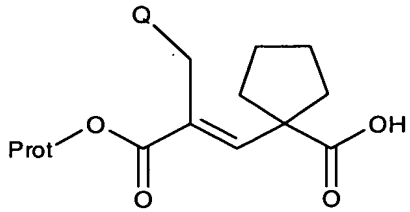
26 A process according to claim 25 further comprising asymmetric hydrogenation of any one of compounds of formula XI, XII or XIII



(XI)

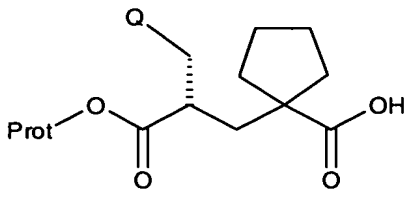


(XII)



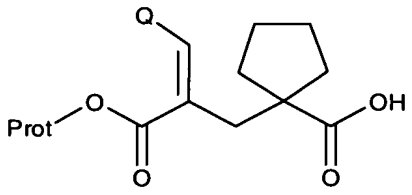
(XIII)

where Q is the substituent on the $C_{1\text{-}6}$alkyl group defined for R^1 in claim 1, to give a compound of formula IIa

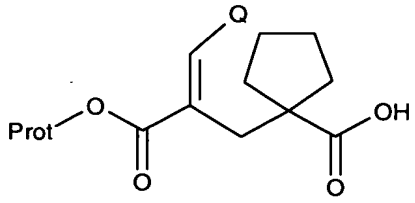


(IIa)

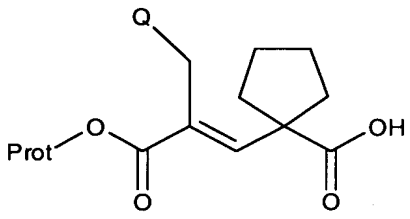
27 A process comprising asymmetric hydrogenation of any one of compounds of formula XI, XII or XIII



(XI)

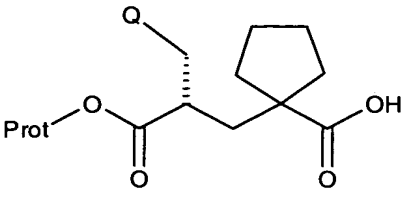


(XII)



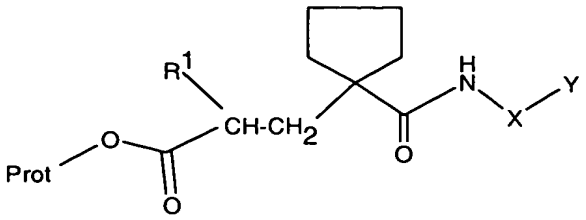
(XIII)

where Q is the substituent on the C_{1-6}alkyl group defined for R^1 in claim 1 and Prot is a suitable protecting group, to give a compound of formula IIa



(IIa)

28 A compound of formula IV



(IV)

wherein R^1, X and Y are as defined in any one of claims 1 to 13 and wherein Prot is a suitable protecting group.